Contributions of the IOM and NCI to Establish a Process for the Development, Commercialization, Assessment, Manufacturing, and Communication about Potentially Reduced Exposure/Risk Cigarettes

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IOM and NCI Documents

- IOM Report:
  - NIH (National Institutes of Health), Institute of Medicine. *Clearing the smoke. assessing the science base for tobacco harm reduction*. Stratton K, Shetty P, Wallace R, and Bondurant S. Washington, D.C., National Academy Press. 2001
- NCI Monograph 13:
  - National Cancer Institute. *Risks Associated with Smoking Cigarettes with Low Machine-Measured Yields of Tar and Nicotine*. Smoking and Tobacco Control Monograph No. 13. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, NIH Pub. No 02-5074, October 2001

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IOM and NCI Documents

- *"This monograph compliments the recently released Institute of Medicine report entitled Clearing the smoke: Assessing the Science Base for Tobacco Harm Reduction. Together, the documents reflect a growing body of research that has explored the impact of products intended to reduce harm in an environment where there is near universal recognition of tobacco's harmful effects. Both documents reflect the need for more research to better understand the feasibility and desirability of developing and marketing products intended to reduce risk, but both also conclude that there is currently no safe tobacco product. "* (NCI Monograph 13, p. ii)
- *"We hope that this evidence will inform any potential recommendations that the Department of Health and Human Services (DHHS) might make to the FTC regarding the cigarette testing method."* (NCI Monograph 13, p. ii)

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Eleven IOM Regulatory Principles

- Ingredients: 1 & 8
- Smoke yield assessment: 2
- Sale of conventional tobacco products: 7
- PREPs: 3, 4, 5, & 6
- Performance standards: 9
- Enforcement powers: 10
- Regulation of drugs and devices: 11

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NCI Monograph Chapters

- Chapter 1: Public Health Implications of Changes in Cigarette Design and Marketing
- Chapter 2: Cigarette Design
- Chapter 3: Compensatory Smoking of Low-Yield Cigarettes
- Chapter 4: Smoking Lower Yield Cigarettes and Disease Risks
- Chapter 5: The Changing Cigarette: Chemical Studies and Bioassays
- Chapter 6: Public Understanding of Risk and Reasons for Smoking Low-Yield Products
- Chapter 7: Marketing Cigarettes with Low-Machine Measured Yields

(NCI Monograph 13, p. X)

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Contribution of IOM and NCI Reports

	IOM	NCI
Guidance		+
Human exposure data vs. machine-smoking data	+	+
Toxicological assessment process	+	
Study populations		+
Requirements for claims	+	
Requirements for claim communication	+	+
Surveillance	+	+
Epidemiology	+	+

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Guidance

- *"Table 5-3 lists the major toxic components in the MS of cigarettes"*[a] (NCI Monograph 13, p. 160)
  - Source: Hoffman et al., 1995
  - [a] This is an incomplete list
- Table 5-4: Carcinogens in Cigarette Smoke (NCI Monograph 13, p. 163)
- Table 5-10 (NCI Monograph 13, p. 177)
  - Source: Pillsbury et al., 1969
- *"Cigarettes with charcoal filter tips deliver MS with significantly lower concentrations of the major ciliatoxic agents, such as hydrogen cyanide and volatile aldehydes."* (NCI Monograph 13, p. 182)

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Toxicological Assessment

"Manufacturers of all PREPs should be required to conduct appropriate toxicological testing in preclinical laboratory and animal models as well as appropriate clinical testing in humans to support the health-related claims associated with each product and to disclose the results of such testing to the regulatory agency." (IOM Regulatory Principle 3)

Emphasis added

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Toxicological Assessment

"Manufacturers of tobacco products, whether conventional or modified, should be required to obtain quantitative analytical data on the ingredients of each of their products and to disclose such information to the regulatory agency." (IOM Regulatory Principle 1)

"All added ingredients in tobacco products, including those already on the market, should be reported to the agency and subject to a comprehensive toxicological review." (IOM Regulatory Principle 8)

"All tobacco products should be assessed for yields of nicotine and other tobacco toxicants according to a method that reflects actual circumstances of human consumption; when necessary to support claims, human exposure to various tobacco smoke constituents should be assessed using appropriate biomarkers. Accurate information regarding yield range and human exposure should be communicated to consumers in terms that are understandable and not misleading." (IOM Regulatory Principle 2)

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Toxicological Assessment

Machine smoking data

- *"... it appears that many of the same changes in cigarette design that reduced machine-measured tar yields also led to a disassociation between the machine-measured yield of the cigarette and the amount of tar and nicotine actually received by the smoker."* (NCI Monograph 13, p. 1)

- *"... tar and nicotine measurements made by the FTC method for current cigarettes have little meaning for the smoker, either for how much he or she will receive from a given cigarette or for differences in the amount of tar and nicotine received when he or she smokes different brands of cigarettes."* (NCI Monograph 13, p. 1)

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Toxicological Assessment

Machine smoking data

- *"There is now also an urgent need for analytical profiles of the toxic and carcinogenic mainstream smoke constituents that are generated under conditions reflecting the puff drawing profiles actually exhibited by humans who smoke these cigarettes that give lower yields as per FTC measurements."* (NCI Monograph 13, p. 1)

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Toxicological Assessment

Machine smoking data

- *"Measurements of tar and nicotine yields using the FTC method do not offer smokers meaningful information on the amount of tar and nicotine they will receive from a cigarette."* (NCI Monograph 13, p. 10)
- *"Variations in the tar and nicotine delivery that result from the known compensatory alterations in smoking behaviors make the current U.S. cigarette tar and nicotine yields as measured by the FTC method not useful to the smoker either for understanding how much tar and nicotine he or she is likely to inhale from smoking a given cigarette or for comparing the tar and nicotine intake that is likely to result from smoking different brands of cigarettes."* (NCI Monograph 13, p. 34)

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Toxicological Assessment

Human studies

- *"Many studies have examined smokers when smoking in a laboratory setting or when asked to switch at specific points in time or to specific brands of cigarettes. These studies offer some insight into how smokers compensate, but may not reflect smokers' behavior when they are switching of their own volition to a brand of their choice."* (NCI Monograph 13, p. 3)

- *"... differences between self-selected populations of smokers or different types of cigarettes."* (NCI Monograph 13, p. 9)

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Requirements for Claims

"In the absence of any claim of reduced exposure or reduced risk, manufacturers of tobacco products should be permitted to market new products or modify existing products without prior approval of the regulatory agency after informing the agency of the composition of the product and certifying that the product could not reasonably be expected to increase the risk of cancer, heart disease, pulmonary disease, adverse reproductive effects or other adverse health effects, compared to similar conventional tobacco products, as judged on the basis of the most current toxicological and epidemiological information."
(IOM Regulatory Principle 7)

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Requirements for Claims

"Manufacturers should be permitted to market tobacco-related products with exposure-reduction or risk-reduction claims only after prior agency approval based on scientific evidence (a) that the product substantially reduces exposure to one or more tobacco toxicants and (b) if a risk reduction claim is made, that the product can reasonably be expected to reduce the risk of one or more specific diseases or other adverse health effects, as compared with whatever benchmark product the agency requires to be stated in the labeling. The 'substantial reduction' in exposure should be sufficiently large that independent scientific experts would anticipate finding a measurable reduction in morbidity and/or mortality in subsequent clinical or epidemiological studies" (IOM Regulatory Principle 4)

Emphasis added

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Requirements for Claim

- *"... the possibility exists that individual product design changes, or future changes in tobacco industry produced nicotine delivery devices, may reduce disease risks in the future. However, the burden of proof for these benefits must remain with those who would make the claims. The proof must integrate both measurements of does and measures of actual biological effect."* (NCI Monograph 13, p. 10)

- *"The very real probability that addicted smokers will seek out and rely upon the promised potential of reduced risk for products that allow continued smoking creates an obligation to require clear scientific proof of harm reduction claims before they are communicated to potential product users."* (NCI Monograph 13, p. 10)

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Claim Communication

"The labeling, advertising, and promotion of all tobacco-related products with exposure-reduction or risk-reduction claims must be carefully regulated under a "not false or misleading" standard with the burden of proof on the manufacturer, not the government. The agency should have the authority and resources to conduct its own surveys of consumer perceptions relating to these claims." (IOM Regulatory Principle 5)

"...the evidentiary base for regulating labeling and advertising must include not only scientific studies related to toxicology and human biology but also scientific analyses of the impact of particular claims, as well as messages and images in advertising and promotional activity, on risk perception and risk communication." (IOM Report, p. 217)

Emphasis added

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Claim Communication

- *"What "Light" and "Ultra Light" come to mean to members of the public is an empirical question that can be revealed by careful survey research."* (NCI Monograph 13, p. 193)
- *"Attention to tar numbers is particularly true among Ultra-Light smokers, a majority of whom say they use these numbers to judge a cigarette's safety."* (NCI Monograph 13, p. 194)
- *"Through most of the 1990s, the Parliament ® campaign consistently used models dressed in white placed in white environments as well as outside..."* (NCI Monograph 13, p. 218)

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Claim Communication

- *"Cigarette advertising is notoriously uninformative… "* (NCI Monograph 13, p. 229)
- *"Occasionally, ads for new technological developments in filter design called attention to the filter, with allusions to filter effectiveness, but almost always without being specific about what constituents of tobacco or its smoke were being filtered, what degree of filtration effectiveness was being realized, or what health or safety consequences were warranted."* (NCI Monograph 13, p. 229)

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Consumer Communication

- *"The cigarette industry has not voluntarily employed its advertising to inform consumers in a consistent and meaningful way about any of the following:*
  1. *The technologies employed in fabricating the products*
  2. *The constituents added in the manufacturing processes"* (NCI Monograph 13, p. 229)
- *"Instead, their advertising for low-yield products has relied on pictures of health and images of intelligence, and has misled consumers into believing filtered products in general, and low-tar products in specific, to be safe or safer than other forms without explaining why."* (NCI Monograph 13, p. 230)

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Surveillance

"The regulatory agency should be empowered to require manufacturers of all products marketed with claims of reduced risk of tobacco-related disease to conduct post-marketing surveillance and epidemiological studies as necessary to determine the short-term behavioral and long-term health consequences of using their products and to permit continuing review of the accuracy of their claims."
(IOM Regulatory Principle 6)

Emphasis added

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Surveillance

"These studies should be designed to assess not only the benefit of the product in reducing the risk of smoking but also the degree to which the product has served to maintain as smokers those who might otherwise have quit and or to recruit new smokers." (IOM Report p. 221-222)

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Surveillance

- *"National mortality rate trends are the cumulative result of all of the changes in smoking behavior over time, changes in cigarette design, demographic changes, and changes in smoking behavior. However, smokers of different types of cigarettes cannot be examined directly for their contribution to these trends."* (NCI Monograph 13, p. 7)
- *"...the desire to reduce disease risk is one of the main factors guiding these choices."* (NCI Monograph 13, p. 194)
- *"...initial cigarette choices, switching as a prelude to quitting, switching as a substitute for quitting, and switching following an unsuccessful quit attempt."* (NCI Monograph 13, p. 194)

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Surveillance

- Issue: Impact of lower tar cigarettes on initiation/cessation
- There appear to be no data that can answer the question of whether the availability of lower tar cigarettes resulted in fewer smokers quitting or more non-smoking starting?

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Epidemiology

Issue: Possible compensation through increasing cigarettes per day

"Epidemiological data corrects for most compensatory smoking behavior (greater number of puffs, more intense smoking, covering dilution holes, etc.), but not for adjustments in cigarettes smoked per day." (NCI Monograph 13, p. 80)

"If compensatory changes include an increase in number of cigarettes smoked per day [CPD], analyses that control for intensity of smoking using CPD produce a risk estimate per cigarette smoked per day, when in reality what is needed is a risk estimate for the total smoking behavior of the smoker as he or she switches brands of cigarettes. The risk should be expressed per smoker rather than per cigarette." (NCI Monograph 13, p. 80)

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Epidemiology

- Possible solution:
  - The best manner in which to evaluate the possible effect of this potential compensatory behavior is to compare the meta-analytical risk both adjusted and unadjusted for CPD
  - RR (lung cancer, F vs. NF) = 0.64 (N=42) unadjusted for CPD
  - RR (lung cancer, F vs. NF) = 0.65 (N=33) adjusted for CPD
  - RR (CVD, F vs. NF) = 0.87 (N=17) unadjusted for CPD
  - RR (CVD, F vs. NF) = 0.87 (N=19) adjusted for CPD

Results derived from meta-analyses conducted by P. N. Lee and E. Sanders

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Epidemiology

Issue: Variability of epidemiological data

- Benhamou (1987): case-control study comparing filter smokers to non-filter smokers cite a relative risk for females, unadjusted for cigarettes/day, of 0.16 (95% CI, 0.04-0.61)
- Alderson (1985): a case-control study comparing filter smokers to non-filter smokers cite a relative risk for males, adjusted for cigarettes/day, of 1.48 (95% CI, 0.81-2.69)

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Epidemiology

- Possible solution
  - Meta-analysis, however, reduces the effect of such variability
    - RR (lung cancer, F vs. NF, unadjusted) = 0.64 (95% CI, 0.61-0.69)
    - RR (lung cancer, F vs. NF, adjusted) = 0.65 (95% CI, 0.61-0.70)
    - RR (CVD, F vs. NF, unadjusted) = 0.87 (95% CI, 0.80-0.94)
    - RR (CVD, F. vs. NF, adjusted) = 0.87 (95% CI, 0.83-0.92)
  - Although the studies included in the meta-analyses for lung cancer are not statistically homogeneous, elimination of studies that contribute to the heterogeneity would result in a lower relative risk

Results derived from meta-analyses conducted by P. N. Lee and E. Sanders

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Epidemiology

- Issue: Confounding
  - *"Smokers of lower tar cigarettes differ in other characteristics from smokers of higher tar cigarettes"*
  - Higher educational level and socioeconomic status which correlates with other positive life style factors such as diet, exercise, etc.
  - Less addicted smokers
  - Voluntary reduction of cigarettes/day
- Possible solution:

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Epidemiology

- Issue: Lack of data that confirm the independent epidemiological studies based on actual lung cancer mortality rates
  - Recent data for younger US male smokers, not cited in Chapter 4, tend to suggest a role of decreased tar in reducing lung cancer risk
  - Recent data for younger UK male smokers, cited in Chapter 4, also suggest a role of decreased tar in reducing lung cancer risk
  - Recent data for younger Australian female smokers, not cited in Chapter 4, tend to suggest a role of decreased tar in reducing lung cancer risk

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Epidemiology

- Issue: Would one expect to see a decline in US lung cancer mortality?
  - Incidence (or mortality) = $0.273(\text{cigts/day}+6)^2(\text{age}-22.5)^{4.5}$
  - Focus on the 1940-1945 birth cohort. In 1960 this cohort would have been starting smoking and, on average, about 50% of the cohort would have been smoking filter cigarettes. If the risk of lung cancer is 65% for filter smokers compared to non-filter smokers, then the overall lung cancer risk for this cohort would have been 82.5%

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Epidemiology

- For a 20 cigarette a day smoker, we have
- $\text{Mortality}_F = 0.273(16.5+6)^2(\text{age}-22.5)^{4.5}$
- $\text{Mortality}_{NF} = 0.273(20+6)^2(\text{age}-22.5)^{4.5}$
- $\text{Mortality}_F/\text{Mortality}_{NF} = (16.5+6)^2/(20+6)^2 = 75\%$
- Therefore, for this cohort, which would have been expected to show the maximum effect, the expected decline would have been in lung cancer mortality would be about 25%
- However, from the CPS-II to CPS-I comparison, we know that between 1960 and 1985, lung cancer mortality increased by 50% for men, and more for women
- Therefore, no effect would be expected in 1985

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Chapter 4 - Key Conclusions

"Existing disease risk data do not support making a recommendation that smokers switch cigarette brands. The recommendation that individuals who cannot smoking should switch to low yield cigarettes can cause harm if it misleads smokers to postpone serious efforts at cessation."

Existing data support the conclusion that quitting smoking will reduce risk more than switching to a reduced tar product, but only after extended cessation.

- RR_{FS}/RR_{CS} (Men) = 0.56 (>21 CPD) after 6-10 years cessation
- RR_{FS}/RR_{CS} (Men) = 0.47 (>21 CPD) after 11-15 years cessation

CPS-II as Cited in Surgeons General Report, 1990, p. 113

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Epidemiology - Key Conclusions

Issue: Age of smokers

"Widespread adoption of lower yield cigarettes by smokers in the United States has not prevented the sustained increase in lung cancer among older smokers."

This conclusion is limited to the United States and to *"older smokers."* Older smokers are those most likely to have had a long smoking history with higher yield cigarettes.

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Chapter 4 - Key Conclusions

"There is no convincing evidence that changes in cigarette design between 1950 and the mid-1980's have resulted in an important decrease in the disease burden caused by cigarette use either for smokers as a group or for the whole population."

The key word is *"important."* As already indicated, quitting smoking will reduce disease risk more than switching to a lower delivery product.

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Chapter 1 - Key Conclusion

"Epidemiological and other scientific evidence, including patterns of mortality from smoking-caused diseases, does not indicate a benefit to public health from changes in cigarette design and manufacturing over the last fifty years."

This conclusion is not completely consistent with the conclusions of Chapter 4, unless the term *"benefit to public health"* implies a decrease in risk greater than that observed.

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Epidemiology

Lessons to be applied

- It is essential to target a significant reduction in risk. Unless this reduction is at least 50%, the approximate reduction in lung cancer risk attributed to about 10 years smoking cessation, it will be difficult to convincingly demonstrate a "benefit to public health."
- Epidemiological surveillance is essential. Moreover, such epidemiological studies must have
  - A large sample size
  - A cohort (prospective design)
  - Excellent control for confounding

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Epidemiology

Lessons To Be Applied

- Identification of **validated** biomarkers of effect is extremely important in order to potentially reduce the amount of time required to obtain meaningful epidemiological data. Validation of such biomarkers must include robust data that demonstrate
  - Clear differences in biomarker level between smokers and non-smokers
  - Clear association of a biomarker with a smoking-related disease

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What the Reports Cannot Provide

- **Regulatory agency**
  - **Implementation, enforcement of its recommendations**
  - **Setting 'standards'**
  - **Independent review and testing**
  - **Approval process**
- **Guidance for commercialization and manufacturing**

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What Can We Learn From These Reports?

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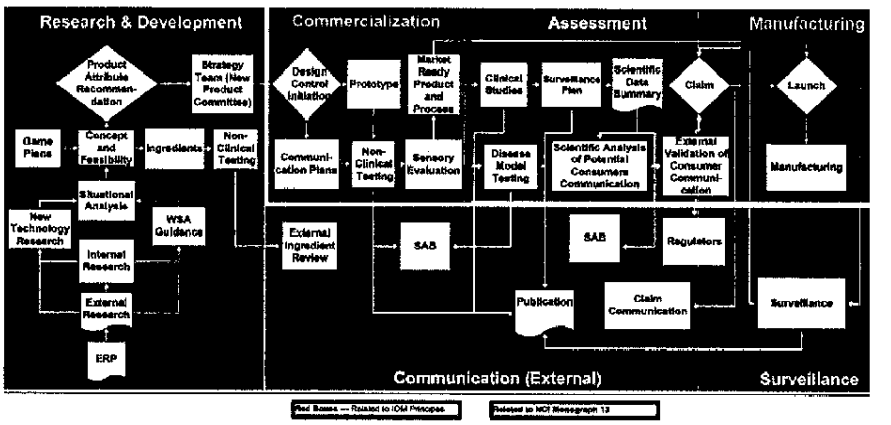
Best Practices to Guide Research and Development, Commercialization, Assessment, Manufacturing, and Communication about Potentially Reduced Exposure/Risk Cigarettes



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Summary

Both Reports: Agree that PREPS make sense and would best be developed and marketed with regulatory framework with cooperation of the industry and public health community

IOM: Future, explicit, scientifically valid concepts for toxicological assessment and claim requirements (practical, guidance)

NCI: Past, implicit, adds guidance, contributes to epidemiology/surveillance

IOM is the primary guide (for Best Practices Framework),NCI considered in the guidance, epidemiology/surveillance

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Backup Slides

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Issues

- Small decrease in risk based on epidemiological studies
  - Lung cancer (filter vs. non-filter) - 36% reduction (42 studies)
  - Lung cancer (low-tar vs. high-tar) - 35% reduction (33 studies)
  - CVD (filter vs. non-filter) - 13% reduction (17 studies)
  - COPD (filter vs. non filter) - 26% reduction (11 studies)

Results derived from meta-analyses conducted by P. N. Lee and E. Sanders

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Issues

- Possible compensation through increasing cigarettes per day
  - "If compensatory changes include an increase in number of cigarettes smoked per day [CPD], analyses that control for intensity of smoking using CPD produce a risk estimate per cigarette smoked per day, when in reality what is needed is a risk estimate for the total smoking behavior of the smoker as he or she switches brands of cigarettes. The risk should be expressed per smoker rather than per cigarette." (NCI Monograph 13, p. 80)